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PHYSIOLOGICAL FACTORS CORRELATING WITH A POSSIBLE CIRCADIAN NADIR IN G-TOLERANCE

A Dissertation

by

BRUCE ALAN WRIGHT

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

December 1998

Major Subject: Interdisciplinary Engineering

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Approved as to style and content by:

Rodger Koppa
(Chair of Committee)

Frances Greene
(Member)

James Rock
(Member)

Vincent M. Cassone
(Member)

Karan Watson
(Head of Department)

December 1998

Major Subject: Interdisciplinary Engineering

ABSTRACT

Physiological Factors Correlating With a Possible Circadian Nadir in G-tolerance. (December 1998)

Bruce Alan Wright, B.S., University of Illinois;

M.S., Texas A&M University

Chair of Advisory Committee: Dr. Rodger Koppa

Circadian variation in athletic performance has been shown to have potentially significant performance consequences for the athlete. This study has attempted to determine whether there is a practical difference between day and night G-tolerance in order to warn pilots of possible adverse consequences due to circadian effects. The subjects' G-tolerance testing times were selected in order to highlight the potential maximum circadian differences. This study leads one to conclude that if there is a circadian effect on a pilot's G-tolerance, it is a small one, or this study would have shown it, and the Air Force should feel more confident to send pilots to fly and fight at night. However, other influences such as lack of sleep and/or extreme levels of stress did seem to have larger effects on pilots' G-tolerance than the proposed circadian effect. Additionally, research on the effect of lighting on suppression of melatonin prior to a nighttime mission should be further investigated.

ACKNOWLEDGEMENTS

To my wife, Joanna, I express my sincere thanks for her love and support during this process. She endured endless days of typing and revision after revision. She is undoubtedly the best editor anyone could ever have, even though I may have grumbled about her red pen from time to time.

I owe an extreme debt of gratitude to my committee chair, Rodger J. Koppa. Dr. Koppa took me on as his student even though I was much older than the usual graduate student. He spent many hours helping me arrange the research as well as organize and analyze the data when it finally arrived. Moreover, throughout the process or writing and revision, he kept me focused on what was important. His suggestions and insight were crucial in making this paper better. I owe Dr. Vincent M. Cassone my heartfelt thanks for his instruction and guidance concerning biological clocks and the circadian influences on hormones. My warm thanks are also extended to Dr. Frances A. Greene, who kept me looking for the bright side even when my data "disappeared" and helped me so much with the interpretation of the statistical analyses. I also want to thank Dr. James C. Rock, who kept me on my toes to be objective and always mindful about research performed in a military setting. He also was very helpful in breaking the tension by talking about airplane "stuff." I also owe thanks to Dr. David M. Simpson for serving as the graduate council representative, and Drs. Paul F. Dahm and Anthony White who helped me with the experimental design and the statistical analysis of the data.

I cannot express enough thanks to the Unites States Air Force for funding my graduate studies while on active duty. I especially want to thank Drs. Jonathan French and Paul Werchan for their support in allowing me access to both the Harry G. Armstrong Laboratory Centrifuge and their ongoing research project. Moreover, Col. James Hawkins form the Brooke Army Medical Center and Dr. Russel Reiter from the University of Texas Health Science Center very kindly made resources of their laboratories available to me. Without generous help of the above persons this project would not have been possible.

Lastly, I want to thank my parents, Alice and Earney Wright. I think they did a pretty good job raising me. They disciplined me when I deserved it, encouraged me when I needed it, and loved me always. Their continual moral support has been, and continues to be, a source of encouragement for me to be a person of determination and self-discipline. Without them, I could not have come this far in my personal as well as educational endeavors. They will always have my love and heartfelt gratitude.

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1. INTRODUCTION AND BACKGROUND

Several measures of human physiological performance vary in a regular manner. Those that vary every 24 hours are called circadian rhythms, while those that have periods shorter than 24 hours or longer than 24 hours are called either ultradian or infradian, respectively (Aschoff, 1981). This physiological variability could have great impact on military and industrial operations as well as profound effects on sporting and other athletic events. The effect of these rhythms on work performance has been described by several researchers, as well as in anecdotal reports, in the sports and aviation literature. This paper will mainly examine the effects of circadian rhythms on physical performance, with emphasis on the military aviation environment.

Military flying is inherently hazardous, but not all of the hazards are from hostile actions. For example, Great Britain found that in the first year of W.W.I, out of every 100 aviators killed, only two had actually met their death in combat. The greatest bulk of deaths were the result of airframe structural failures and pilot carelessness (DeHart, 1985). Fortunately for the pilots, aircraft technology had improved considerably by W.W. II, when manufactures began building fighter airplanes that were more aerodynamically and structurally capable of withstanding high (+6) acceleration or "G." However, these improvements resulted in additional stresses on the pilots.

This dissertation follows the style and format of *Human Factors*.

Higher G forces produced by the new generation of fighter aircraft effected the pilots' performance dramatically because, physiologically, the body was no longer capable of keeping up with the acceleration the aircraft could deliver. As an individual experienced higher acceleration in a head to foot direction ($+G_z$), the blood pressure at the head was reduced, and blood pooled in the lower extremities. Under those circumstances, the heart had to work to compensate for the decreased pressure at head level but was capable of only limited success. Military centrifuge experience has shown that in the absence of any effort on the part of the individual or any anti-G devices, by about 5 G's, the blood pressure at the head level would be reduced to nearly zero, and the individual would start experiencing G-induced loss of vision (blackout) and G-induced loss of consciousness (G-LOC).

According to Burton and Whinnery (1985), as soon as the blackout and G-LOC phenomena were recognized as being produced by high performance aircraft, several methods were devised to improve the pilot's tolerance to them: using the anti-G suit, using the anti-G straining maneuver, and changing the position of the pilot's body relative to application of the G force since an individual more easily tolerates acceleration forces in the chest to back direction designated as G_x. The anti-G suit is a set of trousers covering the abdomen and lower extremities which, when inflated, assists in squeezing blood back toward the heart. The anti-G straining maneuver (AGSM) is defined as a conscious muscular effort by the individual to squeeze blood out of the legs and abdomen toward the heart. By the 1970's, even though several jet aircraft, the F-15 and F-16 in particular, were capable of rapidly attaining and sustaining 9 G's, the pilots

were still utilizing the anti-G methods developed in the 1940's. Advancements in the design of the anti-G suit/valve and enhanced training were allowing the pilots to maintain consciousness but just barely. For the first time in modern aviation history, the aircraft was capable of greatly out-performing the pilot.

In addition to the greater absolute magnitude of the G-force, the F-15 and F-16 introduced several other factors which negatively impacted pilot performance under G. First, digital or "fly by wire" flight controls allowed very rapid (>1G/sec) G onset, faster than cardiovascular responses could compensate. Second, G-limiters allowed full-stick deflection to attain maximum G without risking over-stressing the airframe. That resulted in relatively inexperienced pilots getting themselves into situations for which they were not fully prepared. In effect the airplane couldn't differentiate between an experienced pilot's conscious demand for maximum performance through his/her coordinated manipulation of the control stick and an inexperienced pilot's panicked pull on the control stick. Third, the aircraft were capable of sustaining 9 G's for as long as they had fuel, even though the pilots were not. Fourth, many of these aircraft were two-seaters which meant that either one of the aircrew could be "surprised" by a sudden pull, precluding his/her performance of voluntary counter-measures in anticipation of the acceleration. These limitations of the human in the environment of sustained acceleration were highlighted by the operational experiences of the military services, in particular, increasing G-LOC related accidents.

Pilots now routinely operate near the very limits of their ability to compensate for the high G-environment. Even very minor decreases in their tolerance, such as returning

to flying after a week of being sick and still being weakened, might lead to a G-LOC episode. Indeed, future military aviation operations will probably operate even closer to the very limits of human tolerance. Any factor which compromises the maximum G-tolerance of a pilot may be detrimental when he/she needs it most.

Circadian Rhythms

Many physiological processes in the body exhibit a rhythmic variation irrespective of external cues. These self-sustaining oscillators are normally represented in a sinusoidal fashion where, according to Wever (1979a), the period of a rhythm is defined as the average time after which the arbitrary state reoccurs. These rhythms are called circadian if their periods are about one day long. When a subject does not live under a 24-hour routine but is isolated from all environmental time cues, the rhythms that persist are termed free-running. As Pittendrigh (1981) explains, many self-sustaining oscillators that have periods shorter or longer than 24 hours are synchronized to external rhythms or zeitgebers such as the light/dark cycle which is dictated by the earth's rotation. Furthermore, one oscillator, with a free-running period (t), can couple to and be entrained by a zeitgeber with a different but similar period (T). When entrained, the oscillator's period is changed from t to t^* which is equal to T.

The most commonly referenced circadian rhythms are those of sleep/wake cycles and body temperature. According to Kleitman (1963) "...a 24-hour variation in body temperature was known for a long time. Pieron gave 1842 as the date of the first systematic study by Gierse. Baerensprung ... in 1851, ... noted a coincidence of maxima

and minima for both body temperature and heart rates." Additionally, Kleitman discusses the daily rhythms of respiration, digestion, metabolism, and excretion as well as activity and performance with maxima during daylight and minima at night. Many researchers have demonstrated that certain circadian rhythms have been entrained to periods other than 24 hours. For example, Aschoff and Wever (1981) showed entrainment of sleep/wakefulness cycles for periods as short as 23 hours and as long as 27 hours. Furthermore, a more recent study by Minors et al. (1996) concluded that the circadian rhythm of body temperature could not entrain to a 30-hour "day."

In the textbook *Human Factors for Pilots* (Green, 1991), the authors reported that body temperature varies from an average peak of 36.9° C (98.4° F) in mid-evening to an average low of 36.2° C (97.2° F) in the early morning, and that the period for body temperature remains fairly constant in isolation studies and cannot be easily entrained to different periods. Wever (1979b) found that participants in an isolation study fell into a consistent 25-hour activity cycle, and that the presence of external time cues or zeitgebers, such as light, could easily entrain them to other cycles. The magnitude and direction of those changes were described by Dawson, Lack, and Morris (1992). This team found that a single 4-hour pulse of bright light (12 lux) was able to produce significant shifts in a phase of core temperature rhythm. Light exposure prior to bedtime produced an average phase delay of 2.4 hours, and light exposure following habitual wake up produced a phase advance of 1.5 hours. Similarly, Duffy, Kronauer, and Czeisler (1996) showed that subjects who were placed in a temporal 10-day isolation and exposed to a bright light stimulus would exhibit changes in the circadian timing

dependent on the time of exposure. Subjects exposed to bright light in the late subjective night were phase advanced, and those exposed to bright light early in the subjective night were phase delayed. They concluded that bright light was more effective at altering the human circadian timing system than activity, sleep/wake, social contact, or feeding schedules have. More examples of the effect of light on circadian phase will be discussed in the next section when melatonin is introduced.

Physiological Measures

There are several measures of the physiological status of the body which vary in relation to time of day. These include body temperature, hormone synthesis, and hormone release. The body of data reporting daytime variations in body temperature as reported above is very uniform regarding the amplitude of temperature change as well as the timing of the cycle. This nearly complete uniformity in regard to the circadian cycle for temperature led Trine and Morgan (1995) to conclude: "It appears therefore that the literature on body temperature is consistent, although there are slight variations in the exact time of reported peaks and troughs." In addition to body temperature, one may also examine the release of hormones by the brain or adrenal glands. Several hormones vary in their measurable blood concentration depending on time of day. Measured hormonal variations were used to demonstrate circadian phase advances and delays by Van Cauter et al. (1994). They showed that a single 3-hour bright light pulse shifted the circadian phase of plasma thyrotropin, cortisol, melatonin, and body temperature. The resultant shifts averaged one hour, with delays being larger than advances, and there was little

change in amplitude. The hormones of particular interest for the purposes of this paper include cortisol, epinephrine, norepinephrine, and melatonin. The impact of circadian variations in hormonal release is being felt in several areas of research as evidenced by recent articles regarding cortisol.

Cortisol is a glucocorticoid hormone released from the adrenal cortex which stimulates free fatty acid (FFA) mobilization from adipose tissue, decreases glucose utilization by cells, and increases protein mobilization to yield amino acids for gluconeogenesis in the liver (Powers and Howley, 1994). The hormone is normally released at night, with the greatest measurable amounts seen just prior to the normal waking time for subjects, then declines throughout the rest of the daylight hours. It is also released in response to heavy exercise. In particular, Mills and Marks (1985) found that there was a dose-related increase in cortisol with exposure to higher acceleration levels in the centrifuge. Another group of researchers (Thuma et al., 1995) demonstrated that the circadian variation in cortisol levels "introduced profound quantitative and qualitative errors into the conclusions about the magnitude and existence, respectively, of cortisol responses to exercise." It appears that cortisol can be a good indicator of the level of physical stress placed on an individual if it is compared to a baseline circadian plot.

Two other hormones that have shown circadian variations and have been extensively reported in the literature are epinephrine (E) and norepinephrine (NE). These plasma catecholamines secreted from the adrenal medulla show a circadian peak between 0230 and 0330 hours (Linsell et al., 1985). Their effects on the body include the

alteration of blood pressure, increased mobilization of glucose from the liver, and increased mobilization of FFA from adipose tissue. Additionally, these hormones are associated with strong physical and emotional stimuli. In particular, Lehmann et al. (1982) and Mills (1985) linked higher E levels with elevated mental workloads and higher levels of NE with higher physical workloads. The response of the body to high G-levels in the aircraft produced an elevation of NE levels in a study by Tauri (1991) who tested eight F-4EJ fighter pilots. This finding suggests that NE is called upon by the body to help cope with the increased stress of the acceleration environment.

According to Arendt (1992), melatonin (MT) is a hormone produced primarily at night by the pineal gland in the brain due to the rhythm generated by pacemakers in the hypothalamic suprachiasmatic nuclei (SCN). The linkage between the SCN and the production of melatonin has been reported in animal studies (Cassone et al. 1986; Cassone, 1991) as well as humans. We know that light sensed by the eyes is relayed to the occipital lobes of the brain for processing, but some visual system neurons also project to the SCM. As described by Zhdanova and Wortman (1997), the information regarding light is relayed "from the ganglion layer of the retina to pinealocytes via the optic nerve, the SCN, the lateral hypothalamus, and through the spinal cord by preganglionic fibers synapsing in the superior cervical ganglion. Finally, postganglionic fibers reach the pineal via the nervi conarii." Additionally, according to Cassone (1990), melatonin is synthesized and released by the pineal gland in all vertebrate species studied. The rhythm of synthesis in the pinealocytes follows the uptake of tryptophan that is converted to serotonin and subsequently melatonin. A more in depth discussion of

this process may be found in chapter 18, "The Pineal Hormone-Melatonin," by Zhdanova and Wortman (1997), in the textbook *Endocrinology: Basic and Clinical Principles*.

Endogenous melatonin production can be effected by external factors. Lewy et al. (1980) reported that melatonin secretion is suppressed by bright light (greater than 2500 lux) but not by dim light (500 lux). Additionally, they claim that exposure must be greater than 3 hours per day in duration for the effect to occur. Van Cauter et al. (1994) demonstrated that a single 3-hour light pulse presented under constant routine conditions produced measurable phase shifts of approximately one hour for melatonin and thyrotropin, in addition to expected temperature shifts. Also, Leproult et al. (1997), in their study on sleepiness, performance, and neuro endocrine function, demonstrated clear reduction in plasma melatonin levels when a 3-hour light pulse was given at night after 43 hours of sleep deprivation in a dim indoor light. Earlier, Van Reeth et al. (1994) concluded that something other than light exposure, may exert phase shifting effects on the circadian rhythm of melatonin secretion. They showed that a single 3-hour nighttime pulse of exercise was associated with one- to two-hour phase delay in both melatonin and thyrotropin secretion. Also, Shiota et al. (1996) examined the effect of outdoor exercise on jet lag and suggested that pineal melatonin synthesis and secretion might be mediated by catecholamines generated by intense physical exercise. Additionally, Deacon and Arendt (1995) showed that oral administration of melatonin produced temperature suppression and a phase shift of endogenous temperature and melatonin rhythms.

Other researchers have used varying doses of oral melatonin to shift their circadian cycle. One study by Folkard and Arendt (1993) administered 5 mg of melatonin to shift-workers at bedtime and saw increased alertness during waking hours. The conclusions drawn from the "alertness" were qualified with the preliminary nature of the study and small sample size. Nevertheless, this does suggest that melatonin administration, at appropriate times, might be able to help individuals adapt to circadian cycles which are out of phase with local daylight conditions. Lastly, a study by Middleton et al. (1997) found that 5 mg of melatonin was able to phase shift sleep and core temperature of most subjects. However, the temperature continued to free-run in 4 of 9 subjects.

Athletic Performance

Most of the time, flying an aircraft is not extremely physically challenging. However, in terms of the physiology involved, flying an aircraft in an air combat environment, being exposed to high G-forces, and performing the anti-G straining maneuver (AGSM) is as physically demanding as isometric exercises, weight training, or high intensity cycling. For this reason, G-tolerance and the AGSM are included in this section on athletic performance.

In order to discuss athletic performance, one must first understand how the body derives energy from its fuel, glucose. According to Powers and Howley (1994) in their textbook *Exercise Physiology,* the most important immediate source of energy for muscular contraction is the high-energy phosphate adenosine triphosphate (ATP).

Muscle cells have three ways to produce ATP from fuel: by creatine phosphate formation of ATP (phosphagen system), by the oxidative formation of ATP, and by degrading glucose or glycogen (glycolysis). The formation of ATP through the phosphagen or glycolysis pathways does not involve the use of oxygen and are called anaerobic pathways. The oxidative formation of ATP uses oxygen and is called an aerobic pathway. Aerobic exercises are generally low to moderate in intensity and tend to be long in duration. Since oxygen is used, glucose is completely metabolized into carbon dioxide and water, resulting in a maximum amount of energy being extracted. This level of exercise may be maintained with little muscular discomfort as long as there are oxygen and adequate glucose reserves available. Metabolic reactions that involve energy transfers not requiring oxygen are termed anaerobic. Conversely, anaerobic exercises generally are high in intensity and tend to be short in duration. Because no oxygen is used, glucose is incompletely metabolized into lactic acid that is released in the blood. Accumulation of lactic acid in the blood produces the sensation of muscular fatigue and pain, resulting in the individual's desire to slow down the rate of exercise or discontinue it entirely.

The anaerobic nature of performing the AGSM was examined by Burton et al. (1987). Overall, they saw that the duration of high G exposure, from the G onset until subjects became fatigued, was a very important measure of G-tolerance. Additionally, in reference to acceleration in a head to foot direction or $+G_z$, they concluded that "anaerobic metabolism and isometric exercise physiology are directly related to duration tolerances of fatigue at all levels of $+G_z$." In Burton's study, there was no attempt made

to determine if there were any performance differences dependent on time of day. However, several pilots have related concerns to me personally about their nighttime G-tolerance. These concerns are especially troubling since a large portion of the Air Force mission is now performed at night. Subsequently, the question arises concerning the possible impact of a circadian effect on G-tolerance which may be considered as a type of athletic performance.

Atkinson and Reilly (1996) reported indirect evidence of circadian rhythms effecting sporting performance by noting that most world records in sporting events are broken by athletes competing in the early evening. Additionally, to address concerns about the effects of increased afternoon temperature on athletic performance, he cites swimming studies where the temperature of the water was closely controlled. In these studies swimmers still exhibited their best times for the 100m and 400m races in the late afternoon and early evening. Smith et al. (1997) found that National Football League team performance was effected by circadian rhythms as well. The West Coast teams won more often, and by more points, than East Coast teams. Additionally, they concluded that the circadian effect essentially eliminated any home-field advantage for East Coast teams during Monday Night Football games. A similar study by Steenland and Deddens (1997) found a circadian effect in professional basketball teams traveling coast to coast. The visiting team performed better when traveling west to east, again nullifying the home-field advantage.

While it is well established that there is a specificity of training effect for strength and running, the effect of time of day on training has only recently been

addressed. Hill et al. (1989) attempted to determine if metabolic and cardio-respiratory adaptations to athletic training are greater at the time of day when the training takes place, or if they are uniform throughout the day. This early study looked at 27 college students who trained for 6 weeks on a cycle ergometer either in the morning or afternoon with no training for controls. They saw no time of day effect on maximum performance (VO_2 max) or on performance time, but they did see a slight difference in VO_2 at ventilatory threshold (V_E). The test subjects who trained in the morning had higher V_E in the morning while the subjects who trained in the afternoon had higher V_E in the afternoon. But the difference was not statistically significant. Reinberg et al. (1988) reported not only a peak in isometric grip strength between 1400 and 1900 hours with amplitude of approximately 6% of the 24-hour mean, but also its slowness to adjust to variation in sleep-wake cycles.

When anaerobic power and capacity were examined by themselves, Hill and Smith (1991) found that peak power, as well as the mean power over a 30-second time period, in the evening was 8% higher than at 0300 hours. Perhaps the most interesting study was by Hill et al. (1992) where subjects performed all-out cycle ergometry tests in the morning and afternoon at a constant work rate. Hill found that total work performed in the afternoon was 9.6% greater compared to the morning levels. Furthermore, Hill concluded: "Performance in the afternoon lasts longer, and the amount of work performed before exhaustion is greater, due to increases in both aerobic and anaerobic energy production." Finally, since some researchers found no day vs. night differences in

performance, Atkinson (1996) suggested inadequate test-retest reliability as an explanation for the apparent differences in circadian performance rhythms.

Present State of the Problem

The nature of the modern air combat environment has become so lethal during daylight hours that many missions must now be carried out at night. When one combines the knowledge of human limitations with the recent documentation of variations in muscular or athletic performance throughout the day, the possibility of a nighttime circadian trough in G-tolerance becomes a very real threat to pilot survival. It is in this context that the effect of time of day on one's physical capacity to withstand G-forces was examined.

Hypotheses

1. There is a practical difference between daylight and night G-tolerance in the centrifuge.
2. There is a significant correlation between measured G-tolerance and physiological factors such as concentrations of cortisol, lactate, epinephrine, norepinephrine, and melatonin.

2. METHOD

This study was an addendum to an ongoing study (Circadian Effects on G_Z Tolerance, Project #78145901) at the Armstrong Laboratory, Brooks AFB, TX. The protocol was approved by the Brooks AFB Advisory Committee on Human Experimentation (ACHE) and by the Air Force Office of the Surgeon General Research Oversight Committee as "more than minimal risk with acceptable risk-to-benefit ratio."

Participants

Volunteers were selected from active duty Air Force members or civilian contract employees who were fully qualified centrifuge subjects. All had passed an Air Force flying Class III physical. A total of 12 subjects (11 males, 1 female) participated (see Table 2.1). The subjects' average age was 27.8 years and the range was from 22 to 36 years. Each signed the Brooks Informed Consent Agreement prior to the first test session and were given the option of withdrawing from the study at any time. Each subject who completed both the daytime and nighttime test sessions was paid $75.00.

Table 2.1 Summary of Test Subject Information

Subject #	Age	Gender	Race*	Type**	Centrifuge runs
1	29	M	C	mil/off	500
2	26	M	C	mil/off	300
3	36	M	H	mil/enl	250
4	29	F	B	mil/enl	500
6	23	M	C	mil/enl	27
7	25	M	C	mil/enl	90
8	30	M	C	mil/enl	65
10	26	M	C	mil/off	50
11	32	M	H	mil/enl	1500
12	22	M	H	civ	22

* C = Caucasian
H = Hispanic
B = Black

** mil/off = Military Officer
mil/enl = Military Enlisted
civ = Civilian contract employee

Apparatus

The test facility is the United States Air Force School of Aerospace Medicine Centrifuge located at Brooks Air Force Base in San Antonio, Texas. The centrifuge is the main test apparatus. When a subject is in the test gondola, the centrifuge can produce more than 9 G's of acceleration with an onset rate of 9 G/sec (see Figure 2.1). Each subject was seated at a standard fighter aircraft seat with a 13° seatback angle. The gondola was outfitted with a light bar in front of the subject to allow the subject to assess the vision loss. Additionally, there was a small screen below the light bar onto which was projected a non-critical tracking task (NCT) (see Figure 2.2). The subject had a track ball controller at his/her right hand to make inputs to the NCT (see Figure 2.3).

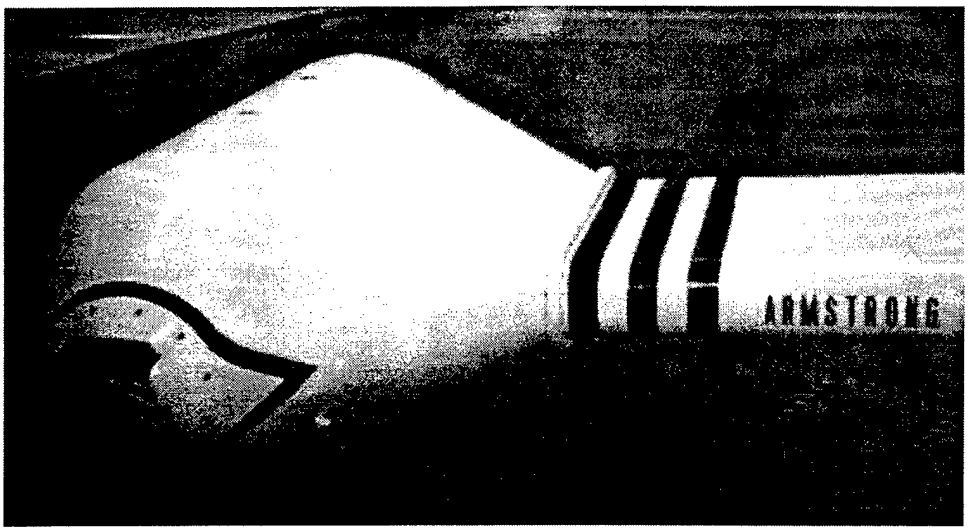

Figure 2.1 U.S.A.F. School of Aerospace Medicine Centrifuge

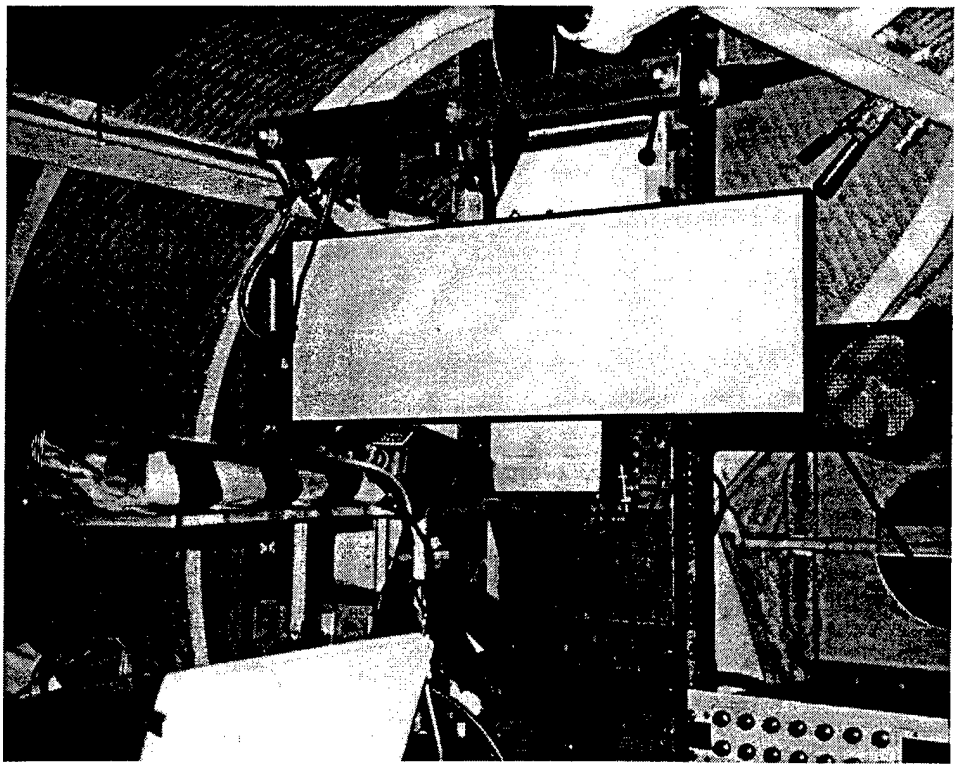

Figure 2.2 Interior of Centrifuge Gondola

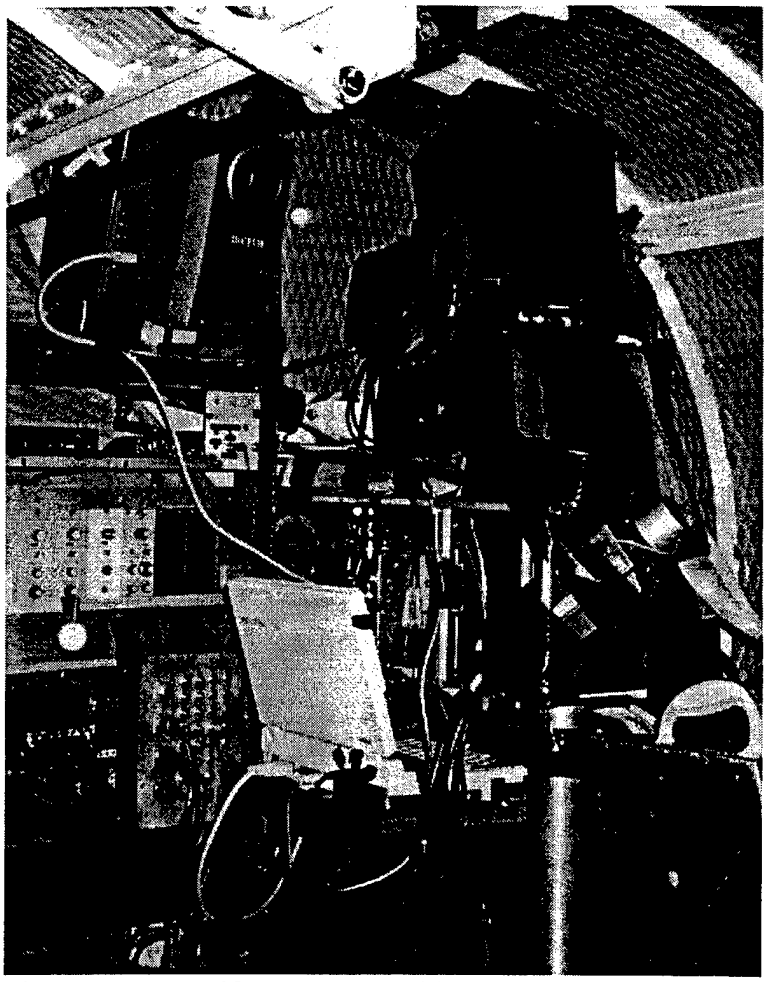

Figure 2.3 Centrifuge Seat, Trackball, and NCT Projector

Procedures

There were two test G sessions, one nighttime (0200-0400 hours) and one daytime (1400-1600 hours). Half of the subjects experienced the nighttime session first and the daytime session second. The other half of the subjects experienced the daytime session first and the nighttime session second. One week was allowed between test sessions. The test sessions began in April 1997. The last session was completed in December 1997. Each test subject experienced the same G profile four times; during the

two test G sessions, as indicated above, and two practice G sessions. The practice G sessions occurred at a convenient time one week before the test G session and served to familiarize the subjects with the requirements of the experiment. All test subjects experienced the same standard air combat maneuver (SACM) profile consisting of a repeating sequence of a +4.5 G_Z exposure for 15 seconds, followed immediately by a +7 G_Z exposure for 15 seconds (see Figure 2.4). This sequence of +G_Z was continued until the volunteer (or the medical monitor or the centrifuge controller) terminated the experiment. Termination was based on 100% peripheral light loss, fatigue, abnormal medical response, G-LOC, or a 10-minute maximum exposure time. During the exposure all volunteers were in the standard upright seat positioned at a 13° seat back angle with a standard Air Force G-suit (military part designation: CSU-13-B/P). One G-awareness period consisting of a single 15-second +4.5 G_Z exposure preceded the SACM profile.

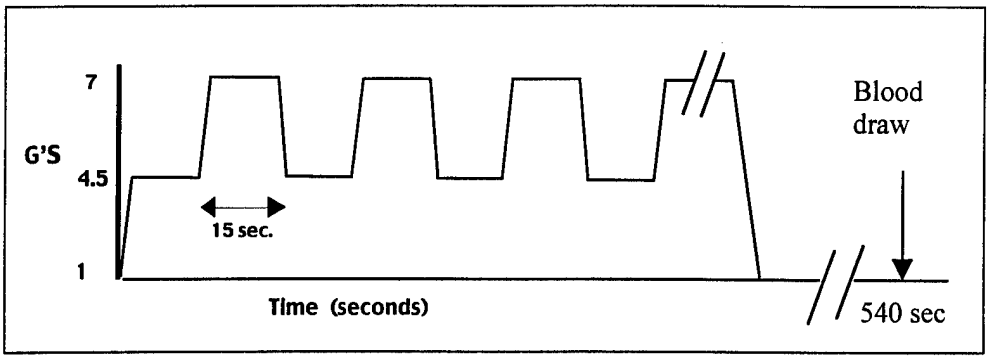

Figure 2.4 Simulated Air Combat Maneuvering Profile

Subjects were asked to complete a log sheet for the 24-hour period before and after the test G session. The log recorded hourly activity, oral temperature, and fatigue data, except while sleeping, as well as sleep/nap duration and quality. Within 15 minutes before the test G session, a 3-cc saliva sample was taken for analysis of melatonin concentration, and a 30-cc blood sample was taken for analysis of epinephrine, norepinephrine, cortisol, lactate, and melatonin concentrations. A certified phlebotomist collected each blood sample. Heart rate was recorded throughout each test session for medical monitoring.

During the G sessions, there was a total of nine minutes of a simple psychomotor task called Non-Critical Tracking or NCT which was incorporated into the standard centrifuge metrics of subjective light loss and heart rate. The NCT test was administered until the subject completed it, regardless of earlier termination of the G session. Upon completion of the NCT, a 30-cc blood sample was taken, then the subject was removed from the centrifuge gondola and a post session NCT test was administered. The NCT data was collected for the main Armstrong Laboratory project and was intended to be analyzed separately by other investigators.

During the test, the centrifuge operators were required to remain as silent as possible, except for essential centrifuge communications so they would not inadvertently influence the motivation of the subjects. The communication was limited to warning test subjects when they were about to change G-levels so the subjects could prepare for the change with their anti-G straining maneuver. A summary of the measures that were taken is provided in Table 2.2.

Table 2.2 Measures to Evaluate Circadian G_Z Tolerance Variation

Test G session ±24 hours	**Test G session ±1 hour**	**During test G session**
Hourly oral temperature	30 cc blood sample	NCT
Sleep/nap duration & quality	NCT	Heart rate
Subjective fatigue	3 cc saliva	Light loss
	Heart rate	Volitional termination time

The intent of the project was to evaluate any circadian degradation of $+G_Z$ tolerance; however, it was very difficult to prevent the effects of sleep loss from interfering with the results. In order to control for the interference of sleep and equate the nighttime and daytime test G sessions in terms of total sleep time, subjects were asked to get to sleep at 1000 the day before their nighttime test G session and to remain asleep until 1700 hours. This closely approximated the Air Forces' crew rest requirement for pilots scheduled for nighttime sessions. The test subjects were to report to the test facility by 1730 hours and were allowed to read, watch movies, etc. until 0030 hours. The pre-test requirements began at 0100 hours and the G test sessions began at 0200 hours. Post-test requirements were performed in the hour immediately following the test session. The test subjects were discouraged from driving themselves home after their nighttime test session and were allowed a day of leave to overcome the effects of circadian disturbance.

It was required that during the daytime test session the subjects got their normal nights sleep of approximately seven hours. They reported to work for their normal duty schedule on the test day, except they had to be available at 1300 hours for the pre-test requirements and for the G test sessions that began at 1400 hours. Post-test requirements

were performed in the hour immediately following the test session. A summary of the requirements for the training, nighttime test, and daytime test sessions is provided in Table 2.3.

Table 2.3 Summary of Requirements for G Test Sessions

Week before test session	**Nighttime test session**	**Daytime test session**
15 NCT lab training sessions	Bed by 1000	Bed by 2300
15 NCT centrifuge training sessions	Report to lab by 1730	Report to work by 0730
1 practice g session and NCT	Remain awake all evening	Remain at work all day
	Pre-test 0100	Pre-test 1300
	Test 0200	Test 1400
	Post-test one hour after test	Post-test one hour after test

Design

This study was analyzed as a repeated measures Latin Square design. The independent variables were the daytime (control) and nighttime (experimental) testing times. Each subject experienced both daytime and nighttime test conditions. Initial exposures were counterbalanced such that half of the subjects experienced the daytime test session first and half experienced the nighttime session first. The dependent variables were duration for the SACM session, and pre-test and post-test blood concentrations of epinephrine, norepinephrine, cortisol, lactate, and melatonin. The SACM duration was the time in seconds from acceleration above 1 G until one of three things happened: the test session was terminated by the subject activating the brake,

maximum time for the session had passed, or the medical monitor decided that the test session had to be stopped. Epinephrine, norepinephrine, and cortisol were used as dependent variables because they are stress hormones that are released in response to strong physical or mental stimuli. Their blood concentration also changes according to the time of day as discussed in the background section. Lactate is a by-product of anaerobic metabolism, and its accumulation in the blood is an indication of physical stresses reaching high levels. Melatonin is a hormone associated with the onset of sleep, and we would expect its highest concentrations at night as discussed in the background section. The list of dependent variables and their units of measurement is presented in Table 2.4.

Statistical analysis consisted of t-tests of related means for each dependent variable. Additional analyses examined possible correlation between G-tolerance duration and physiological measures, and among various physiological measures.

Table 2.4 Dependent Variables With Units of Measurement

Dependent Variable	**Units**
SACM duration	seconds
pre- and post-exposure concentrations of:	
norepinephrine	pg/ml
epinephrine	pg/ml
cortisol	µg/ml
lactate	mmol/L
melatonin	pg/ml

Hormonal Assays

The Brooke Army Medical Center (BAMC) Area Laboratory in San Antonio performed the analyses on the collected blood samples for norepinephrine, epinephrine,

cortisol, and lactate concentrations. Dr. Russell Reiter's laboratory at the University of Texas Health Science Center (UTHSC) in San Antonio performed the assays for melatonin in saliva and blood samples.

Plasma melatonin levels were measured using a commercially available procedure from Stockgrand, Department of Biochemistry, University of Surrey, Guilford, Surrey, UK, using an antimelatonin antiserum raised in sheep. The lower limit of sensitivity is 2 pg/ml; the precision of the assay averages 10% in the range of physiological concentration.

Plasma cortisol levels were determined using a kit from Abbott Labs Inc., Abbott Park, IL, using the fluorescent polarization immunoassay on the Abbott Labs TDXFLX machine. The lower limit of sensitivity is 0.64 µg/dl. The intra-assay coefficient of variation is <7.8% in the physiological range. The interassay coefficient of variation is <6.4% in the physiological range.

Plasma catecholamines were measured using high performance liquid chromatography with electrochemical detection. The equipment used was the Bio-Rad Laboratories HPLC test apparatus from Bio-Rad Laboratories, Hercules, California; Catalog Number 195-6078. The limit of sensitivity for epinephrine is 10-2000 pg/ml; the intra-assay coefficient of variation averages <7.8% in the range of physiological concentration; the interassay coefficient of variation averages <7.2% in the range of physiological concentration. The limit of sensitivity for norepinephrine is 25-2000 pg/ml; the intra-assay coefficient of variation averages <4.2% in the range of

physiological concentration; the interassay coefficient of variation averages <3.7% in the range of physiological concentration.

Lactate was measured spectrophotometrically using the Vitros 700 system and the Vitros LAC slide kit from Johnson & Johnson Clinical Diagnostics, Rochester, NY. The lower limit of sensitivity is 0.5-12 mmol/L; the intra-assay coefficient of variation averages <0.2% in the range of physiological concentration; the interassay coefficient of variation averages <1.8% in the range of physiological concentration.

3. RESULTS

A total of 10 subjects finished the study. Two subjects were removed from the initial group of 12 for all statistical analyses because both of them violated the test protocol, and all information regarding their performance was considered to be unreliable. We were unable to replace these two subjects for three reasons: all data had already been collected, blood samples were already processed through the various laboratories, and centrifuge time had already been re-allocated to other research projects.

Subject number 5 was removed because he terminated his test session at exactly the same time for both the daytime and nighttime test sessions. According to the Armstrong Laboratory experimental protocol, termination was to be "based on 100% peripheral light loss, abnormal medical response, fatigue, or G-induced loss of consciousness (GLOC)." After reviewing the videotape of his test sessions, the team of researchers concluded that he did not perform to his maximum potential but instead terminated his sessions at a predetermined number of peaks (both times the subject terminated the session as the centrifuge operator informed him that he was about to go to 7 G's again).

Subject number 9 was removed because he did not get enough sleep before his daytime test session (less than 2 hours of sleep for the previous 3 nights) and was exceptionally well rested for his nighttime session (10 to 12 hours of sleep for the previous 2 nights). Again, the Armstrong Laboratory experimental protocol stated: "It is assumed that during the daytime test session that the subjects will get their normal

night's sleep, approximately 7 hours. They will be requested to go to sleep at their normal time and arrive at work as usual."

The raw data in Table 3.1 shows G-tolerance performance (duration) and the results from laboratory analyses of subjects' pre-run and post-run blood samples. Several missing values in the table are the result of one or more of the following: catastrophic equipment failure, contaminated samples, and missing samples.

Duration

When day and night durations for centrifuge runs were graphically contrasted by subject (see Figure 3.1), no definite trends were evident. Subjects varied in their performance (duration) to a greater extend during the day than at night. Six of the subjects performed better during their daytime sessions while the remaining four subjects performed better during their nighttime sessions. Overall, the mean duration for day sessions was almost the same as for the night sessions (320.3 sec., 319.0 sec., respectively). However, Figure 3.1 shows a somewhat greater variance for day vs. night (sd=113.42 sec., sd=105.2 sec., respectively).

When day and night duration for centrifuge runs were graphically contrasted, in Figure 3.2, by subjects' previous number of centrifuge runs, no trends were seen. Overall, subjects with 250 or more previous runs did not seem to have any advantage over the less experienced subjects when it came to their G-tolerance duration.
The time of day and duration data was analyzed using t-tests in a series of five 2x2 Latin Squares. The results are reported in Table 3.2.

Table 3.1 Raw Data for the Circadian G-tolerance Study

Subj #	Dur	D/N	Pre/post	NE	Epi	Cort	Lact	Mel B
1	532	day	pre	515	86	8.9	1.9	10.2
			post	2030	152	19	3	11.5
	438	night	pre	428	127	15	1.1	15
			post	1261	160	24	2.8	18.9
2	314	day	pre	271	43	11	1.2	11.8
			post	753	52	14	3	16.6
	273	night	pre	213	38	5.8	0.7	46
			post	566	71	13	2.2	61.9
3	314	day	pre	327	64	8	0.8	28.9
			post	873	86	16	2.9	40.1
	187	night	pre	379	59	6.9	0.8	56.2
			post	574	63	19	2.4	112
4	218	day	pre	**	**	8.5	1	5.38
			post	379	27	15	2.5	5.11
	375	night	pre	338	18	4.9	0.8	11.3
			post	481	30	16	2.7	8.2
6	250	day	pre	500	59	12	0.9	12.1
			post	933	213	27	4.8	14.6
	219	night	pre	397	99	5.6	0.8	71.3
			post	730	113	19	4.9	83.4

* Dur = duration of exposures on the centrifuge during testing in seconds
D/N = day or night exposure
Pre/post= time when blood and saliva samples were taken
NE = norepinephrine in pg/ml
Epi = epinephrine in pg/ml
Cort = cortisol in ug/ml
Lact = lactate in mmol/l
MelB= melatonin in blood in pg/ml

** missing values

Table 3.1 (continued)

Subj #	Dur	D/N	Pre/post	NE	Epi	Cort	Lact	Mel B
7	124	day	pre	448	40	4.7	1.1	5.26
			post	856	88	13	6.8	4.29
	157	night	pre	436	73	6.2	0.8	191
			post	719	172	16	7	22.7
8	314	day	pre	356	29	6.1	0.7	4.69
			post	526	35	16	2.2	5.11
	431	night	pre	352	27	1.3	1.4	9.84
			post	699	56	11	2.4	15.1
10	365	day	pre	317	92	9.5	2.3	2.58
			post	1017	115	23	3.5	2.83
	412	night	pre	349	40	4.5	1.1	17.1
			post	758	109	**	3.1	23.7
11	330	day	pre	516	52	9.2	1.2	**
			post	995	57	**	**	**
	307	night	pre	346	18	3.4	0.9	7.75
			post	537	33	12	1	6.71
12	442	day	pre	338	64	6.7	1	5.37
			post	1390	113	24	5.5	6.12
	391	night	pre	429	62	1.2	0.9	3.97
			post	506	68	25	2.9	27.1

* Dur = duration of exposures on the centrifuge during testing in seconds
D/N = day or night exposure
Pre/post= time when blood and saliva samples were taken
NE = norepinephrine in pg/ml
Epi = epinephrine in pg/ml
Cort = cortisol in ug/ml
Lact = lactate in mmol/l
MelB= melatonin in blood in pg/ml

** missing values

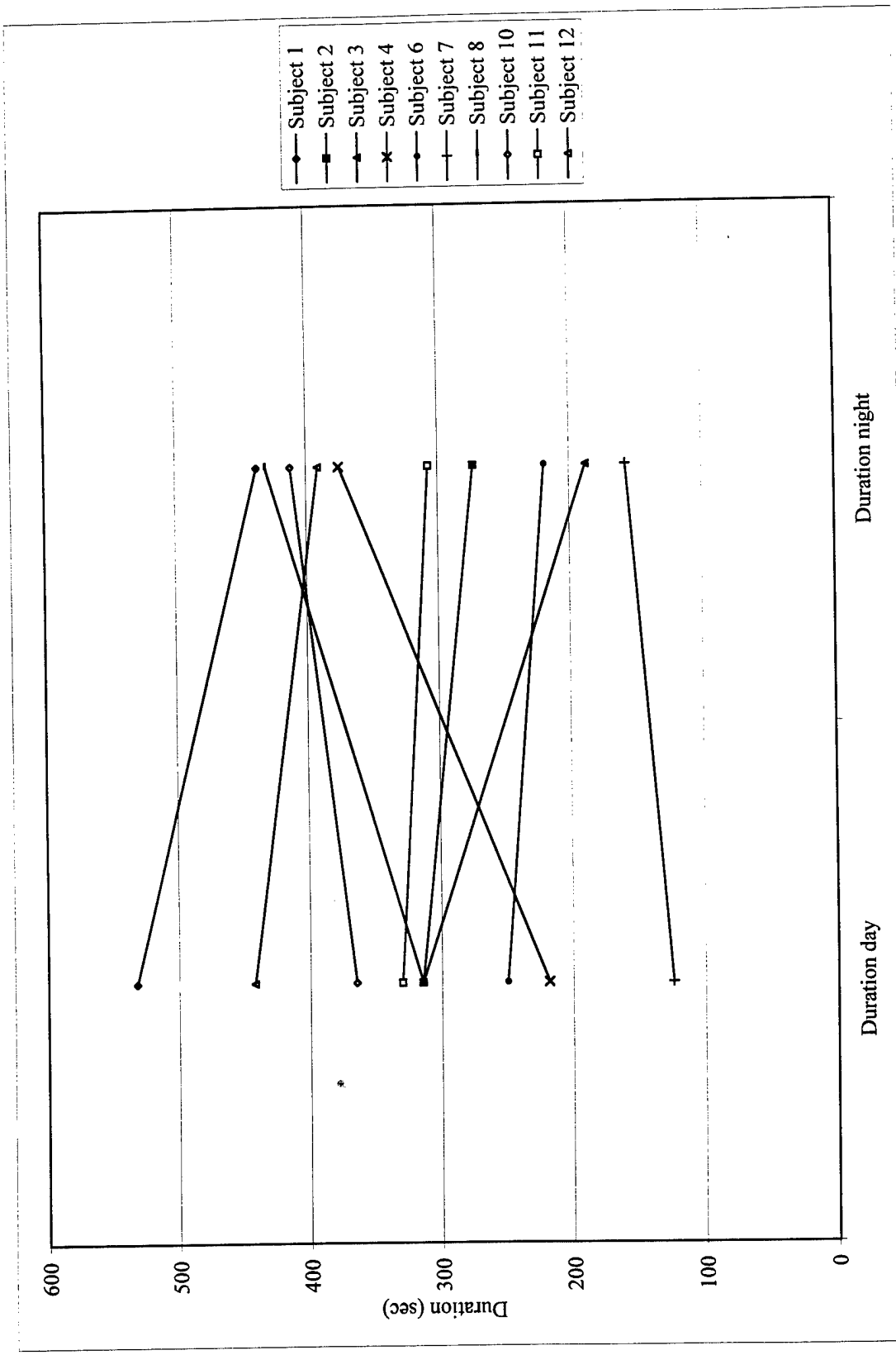

Figure 3.1 Effect of Time of Day on Centrifuge Performance

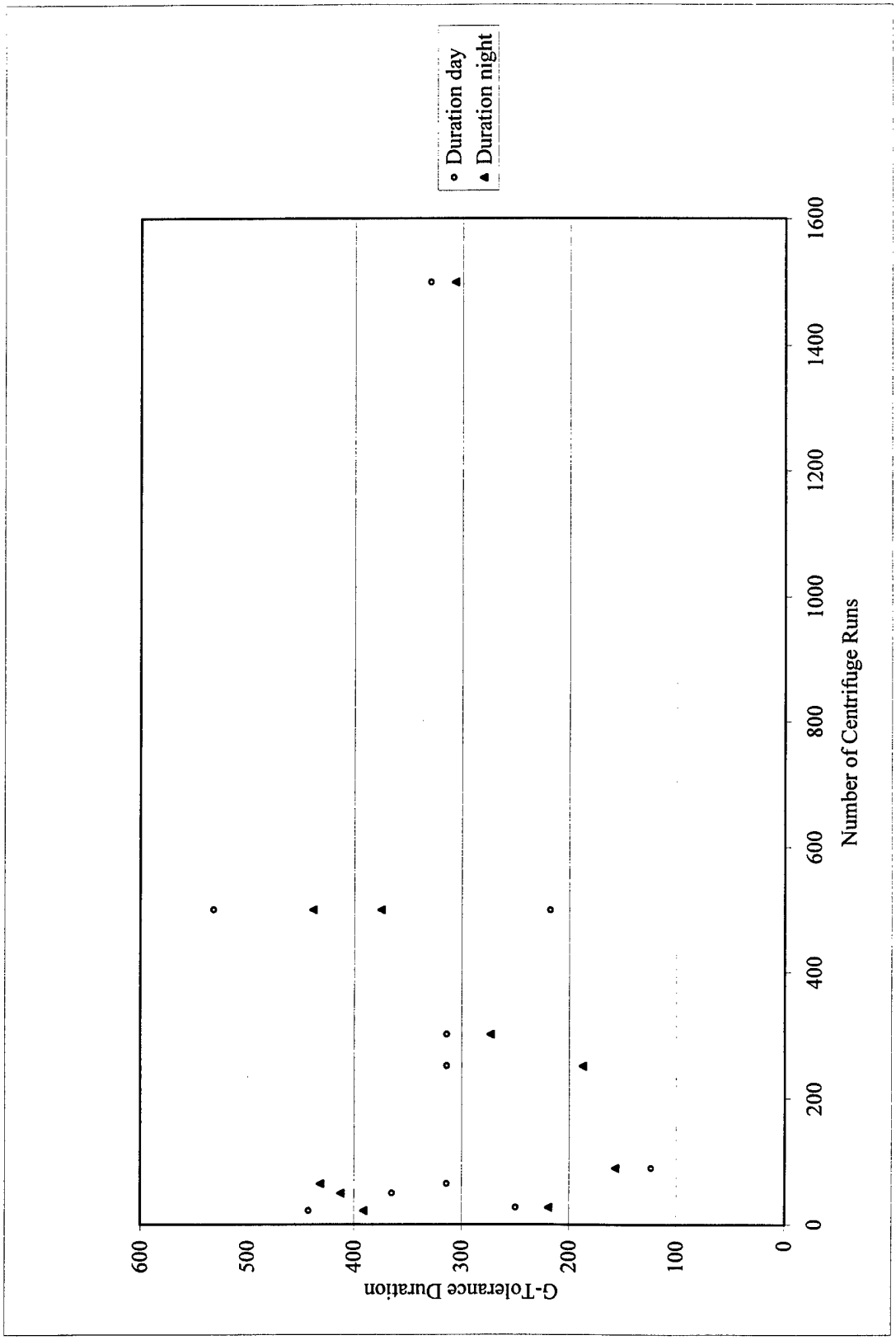

Figure 3.2 Day and Night G-tolerance Duration vs. Prior Centrifuge Experience

Table 3.2 Results of a Two-period Crossover Study Carried out in Five Latin Squares

		Session D=daytime N=nighttime			
Square	**Subject #**	**1**	**2**	**T=Sum**	**D=Difference**
1	4	218 D	375 N	593	-157
	1	438 N	532 D	970	-94
2	6	250 D	219 N	469	31
	2	273 N	314 D	587	-41
3	8	314 D	431 N	745	-117
	3	187 N	314 D	501	-127
4	10	365 D	412 N	777	-47
	7	157 N	124 D	281	33
5	11	330 D	307 N	637	23
	12	391 N	442 D	833	-51

		Sums		Differences	
Order	Sample size	Mean	sd	Mean	sd
DN	n=5	$\overline{T}_1$ =644	s_{T_1} =123.658	$\overline{D}_1$ =-53.4	s_{D_1} =83.335
ND	n=5	$\overline{T}_2$ =634.4	s_{T_2} =272.49	$\overline{D}_2$ =-56.0	s_{D_2} =60.531

$$t_{treatment} = \frac{\overline{D_1} - \overline{D_2}}{s_D}\sqrt{\frac{n}{2}} = 0.056$$

$$t_{sequence} = \frac{\overline{D_1} + \overline{D_2}}{s_D}\sqrt{\frac{n}{2}} = 2.375$$

$$s_D = \sqrt{\frac{s_{D_1}^2 + s_{D_2}^2}{2}}$$

$$t_{carryover} = \frac{\overline{T_1} - \overline{T_2}}{s_T}\sqrt{\frac{n}{2}} = 0.071$$

$$s_T = \sqrt{\frac{s_{T_1}^2 + s_{T_2}^2}{2}}$$

*The analyses used above follow the procedure described by Joseph L. Fleiss in chapter 10.1, "The Two-Period Crossover Study," in *The Design and Analysis of Clinical Experiments.*

The first test ($t_{treatment}$) measured the treatment effect, comparing daytime to nighttime duration. The result was not significant at the .05 level ($t=0.056$, $p>0.25$) as expected from the data in Figure 3.1. The second test ($t_{sequence}$) measured the sequence effect, comparing 1st session's to 2nd session's duration regardless of the time of day. The result was significant at the .05 level ($t=2.375$, $p=0.05$). The third test ($t_{carryover}$) measured the carryover or residual effect on duration from session 1 to session 2, regardless of the time of day when the first session took place. The result was not significant at the .05 level ($t=0.071$, $p>0.25$) which means that the carryover, if any from day to night is equivalent to the carryover from night to day. This is good news since, according to Fleiss (1986), the data from the second session would have to be dropped if there was a differential carryover effect.

Blood Components

As a first step in investigating the relationships between various pre and post blood components and subjects' time of day exposure, the data was plotted as shown in Figures 3.3 through 3.7. For comparison purposes, the normal ranges for catecholamines, melatonin, lactate, and cortisol are shown in Table 3.3. The ranges for melatonin are from Chapter 18 of the 1997 edition of *Endocrinology: Basic and Clinical Principles.* The ranges for the remaining blood components are from Table 41-20 in the appendix of the 1994 edition of *Tietz Textbook of Clinical Chemistry.* It can be seen in Figure 3.3 that both daytime and nighttime pre-exposure levels of norepinephrine are well within the normal range. Similarly, Figures 3.4 to 3.7 show pre-exposure levels of

the respective blood components to be within the normal physiological range, with exception of epinephrine and nighttime cortisol that were elevated for several subjects. With few exceptions, post G session blood concentrations of the selected hormones and lactic acid are always higher than pre G session concentrations. This is not unexpected given strong body of research, discussed in the Introduction, which agree with the above findings.

Table 3.3 Normal Ranges for Catecholamines, Cortisol, Lactate, and Melatonin

Blood Component	**Normal Range**
Norepinephrine	120-680 pg/ml
Epinephrine	<60 pg/ml
Cortisol	3-23 µg/dl (day)
	<0.5 µg/dl (night)
Lactate	0.5 – 1.3 mmol/L
Melatonin	1-6 pg/ml (day)
	10-300 pg/ml (night)

Because Figures 3.3 through 3.5 suggested that subjects were significantly stressed during their centrifuge runs, simple t-tests comparing all subjects' pre-run to post–run stress related hormone levels (regardless of the time of testing) were performed. The results are presented in Table 3.4.

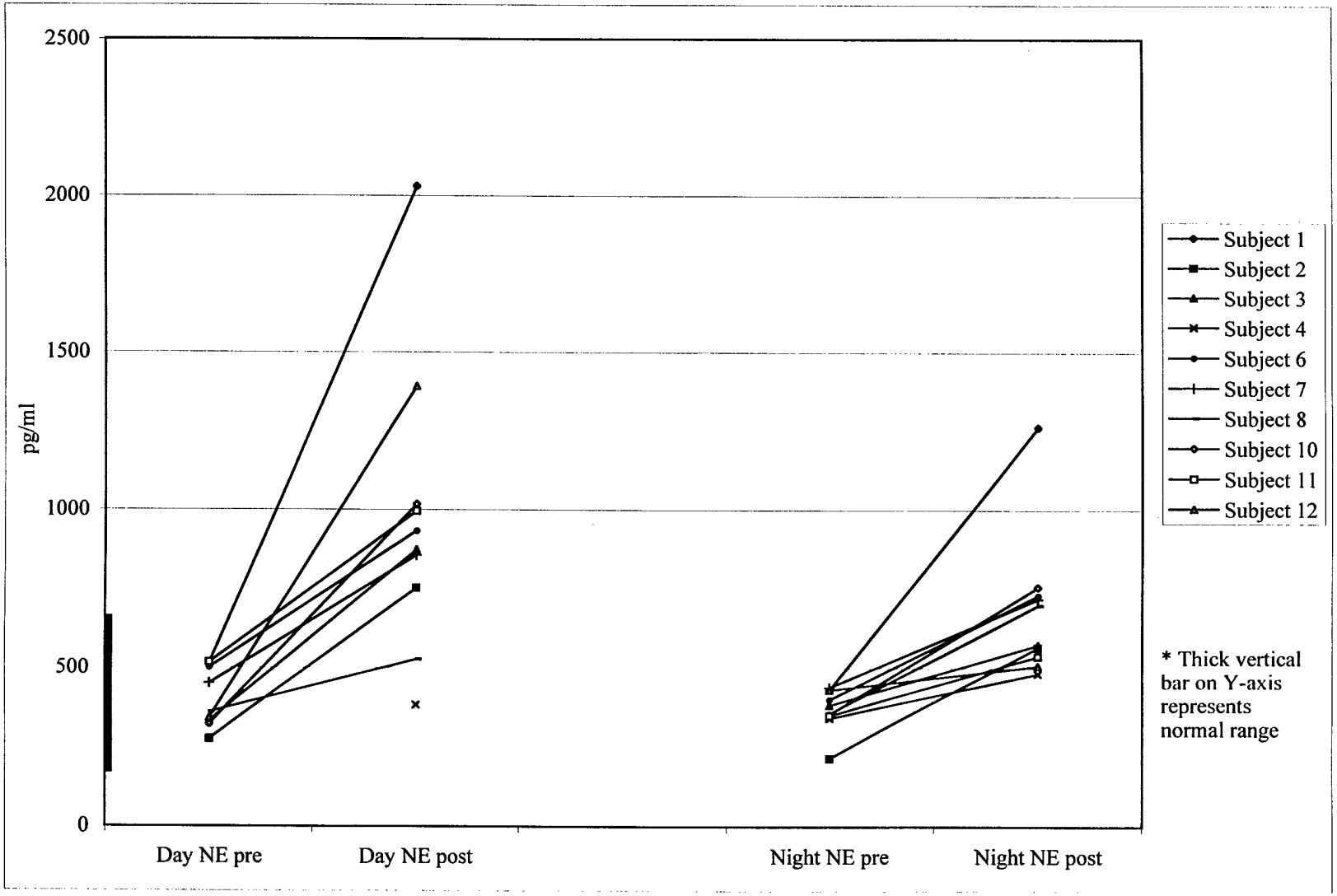

Figure 3.3 Norepinephrine Plot

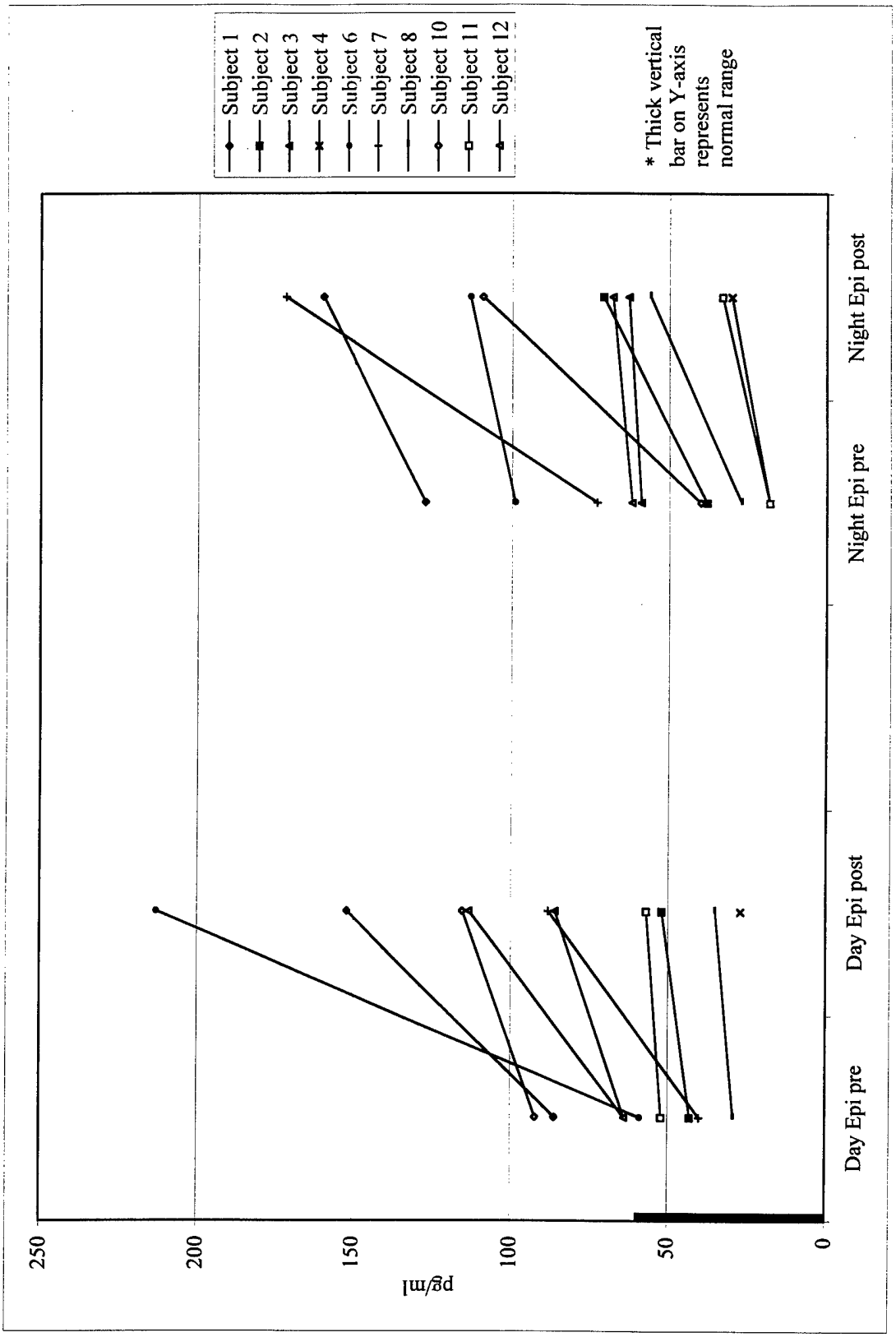

Figure 3.4 Epinephrine Plot

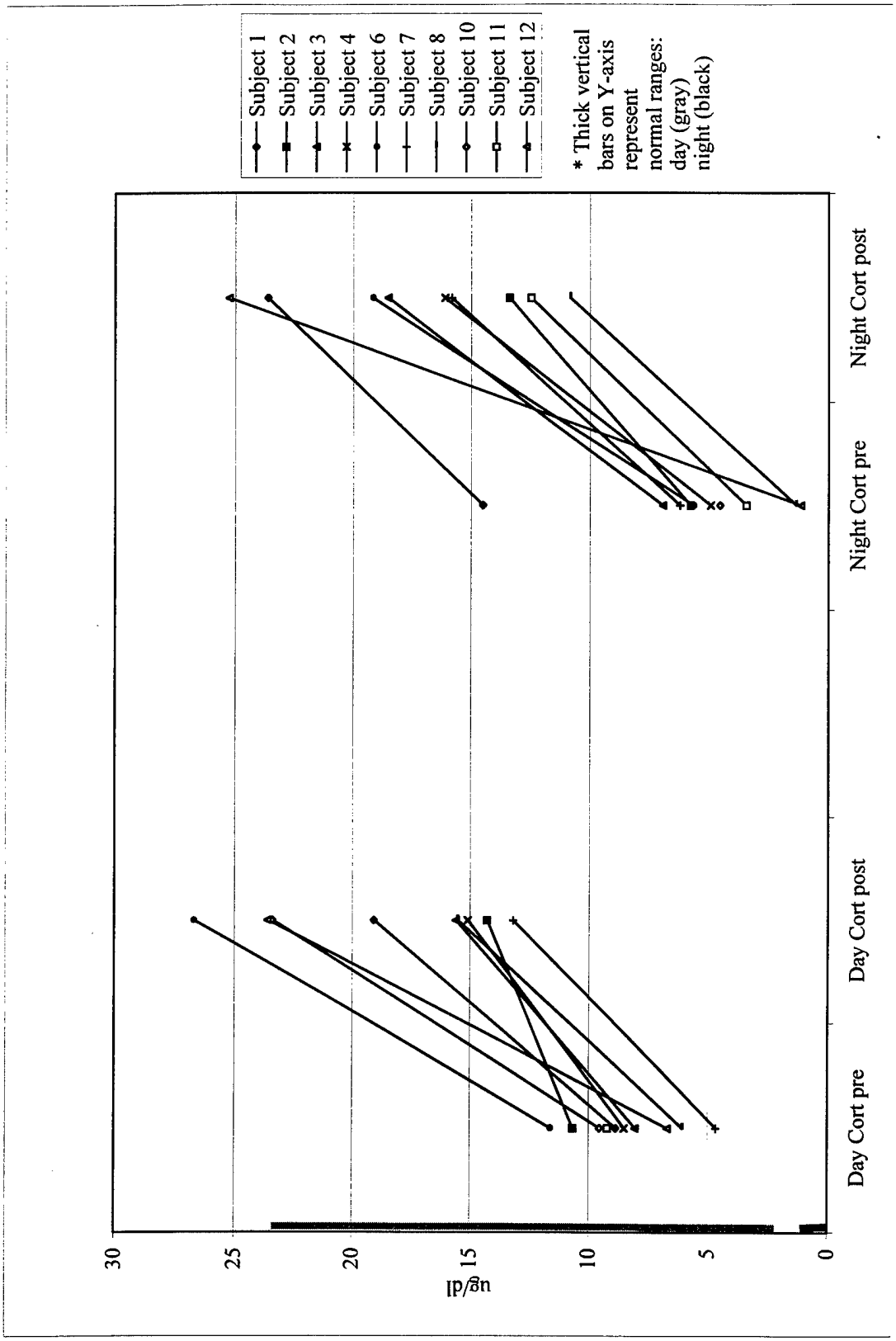

Figure 3.5 Cortisol Plot

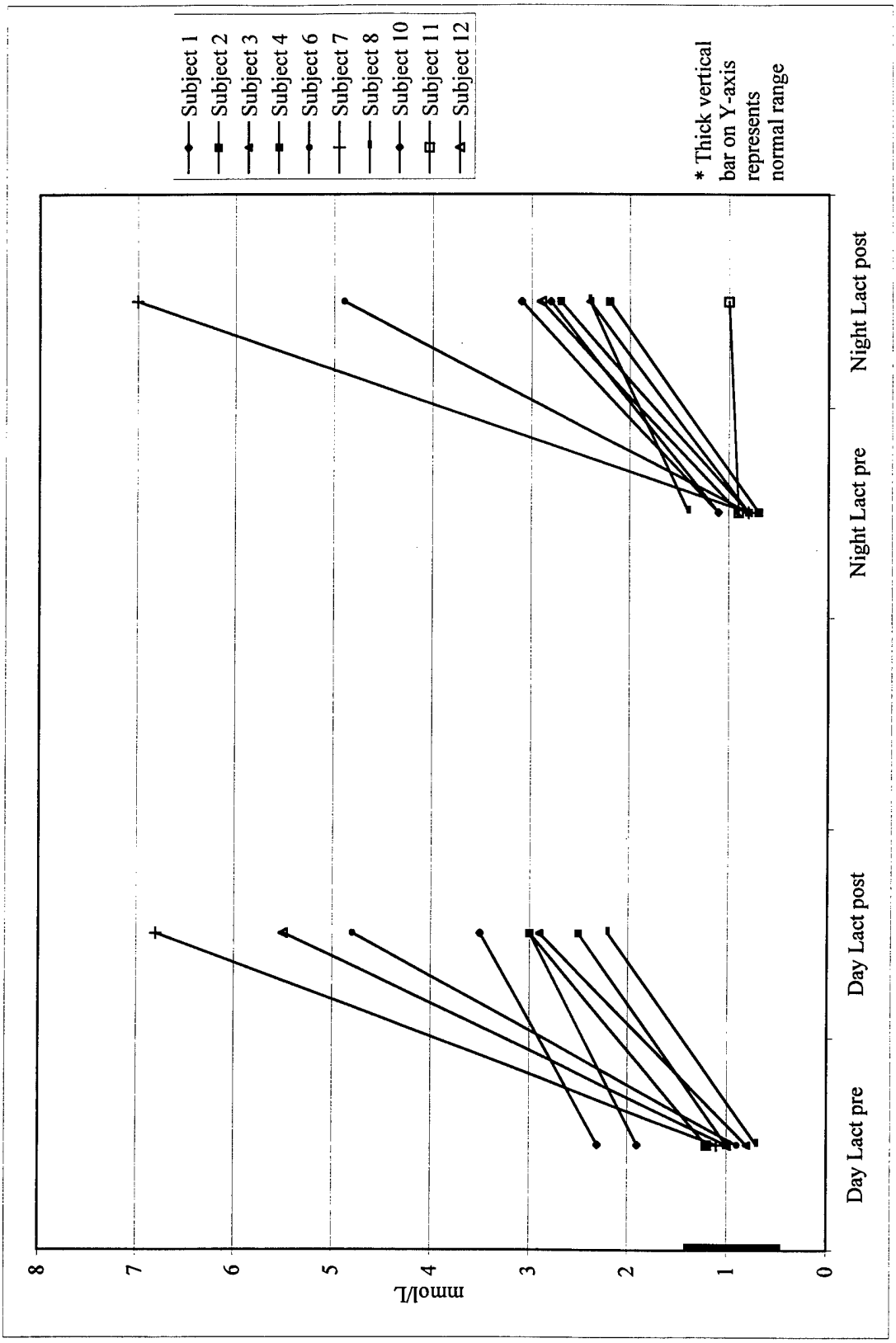

Figure 3.6 Lactate Plot

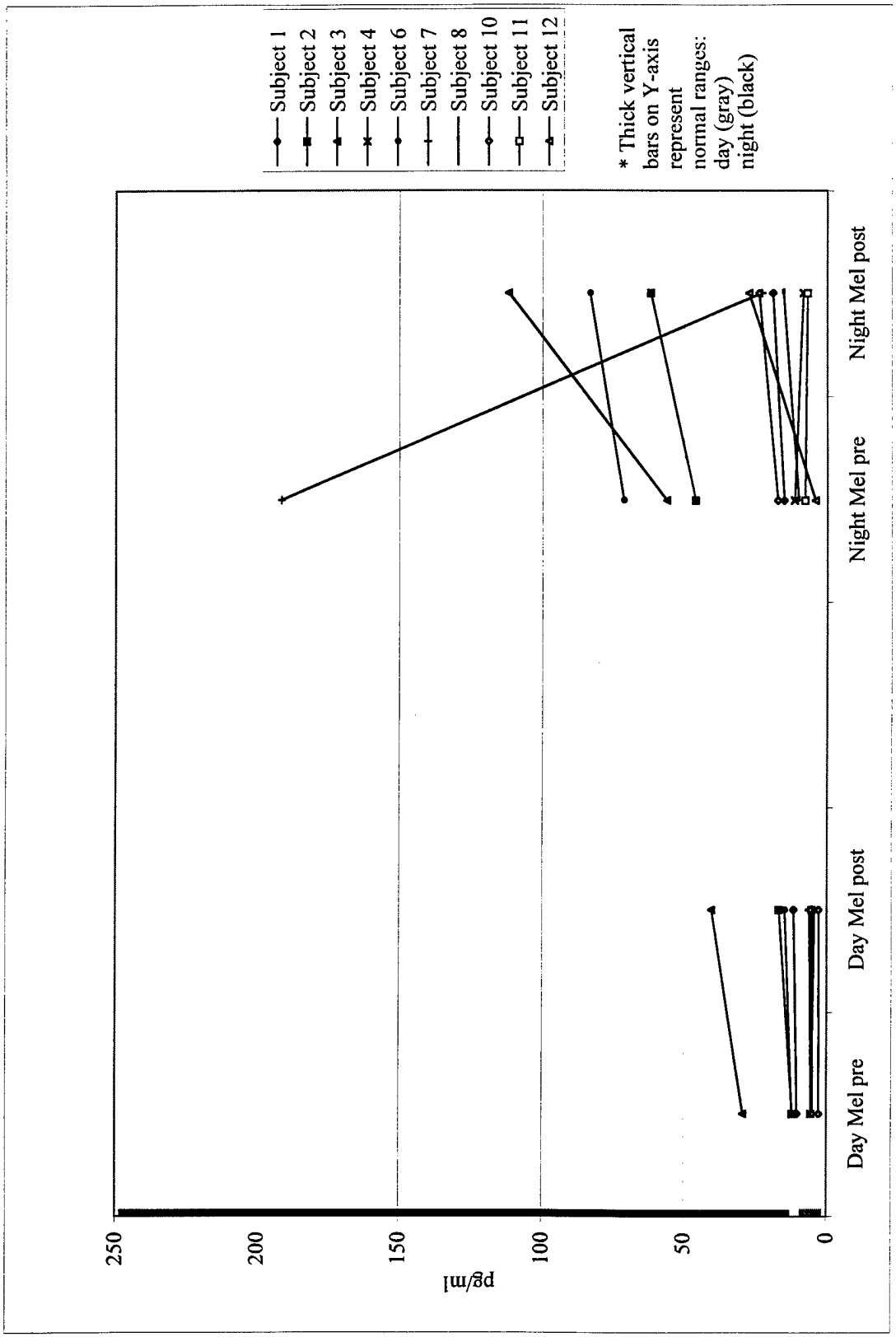

Figure 3.7 Melatonin Plot

These findings confirm the conclusions of Lehmann (1982), Mills (1985), and Tauri (1991) that norepinephrine is more associated with physical stress than epinephrine, which is more often associated with cognitive stress. Moreover, cortisol results agree with Mills and Marks (1982) and Mills (1985), as well as the textbook examples in *Exercise Physiology, Energy, Nutrition, and Human Performance* (McArdle, Katch, Katch, 1991), that cortisol is a reliable indicator of physical stress.

Table 3.4 Comparison of Pre and Post Stress Hormone Levels

Hormone	**Test group**	**t-value**	**p-value**
Norepinephrine	Day and Night	5.052	<0.0001
	Day	3.664	0.0019
	Night	4.239	0.0005
Epinephrine	Day and Night	2.689	0.0102
Cortisol	Day and Night	7.927	<0.0001
	Day	5.951	<0.0001
	Night	5.931	<0.0001

Furthermore, the accumulation of lactate in the blood after daytime and nighttime test sessions reinforces the supposition of very high level of physical stress for these subjects. This highly significant difference was apparent whether the data was examined without regard to time of day ($t = 6.437$, $p<0.0001$) or separated into daytime ($t = 5.0$, $p<0.0001$) and nighttime ($t = 4.166$, $p<0.0006$) test sessions. Subjects were highly anaerobically stressed while performing the anti-G straining maneuver (AGSM) as previously reported by Burton et al. (1987).

After examining Figures 3.3 through 3.7, it was also concluded that many significant relationships of pre-test levels of various blood components to G-tolerance

were possible, but correlations were low except for the relationship of melatonin to duration (r = -0.53) and of cortisol to epinephrine (r = 0.61). The multivariate correlation matrix for all pre-exposure blood components and for duration is presented in Table 3.5. Please note that this set of correlations used only observations that had no missing values for all variables in the analysis. Additionally, post-exposure correlations of blood components and duration are not presented since they would not have any value in predicting pilots' performance.

Table 3.5 Correlation Matrix Using Pre-Exposure Blood Samples

Variable	Duration	NE	Epi	Cortisol	Lactate	Mel Blood
DUR	1.00					
NE	-0.01	1.00				
Epi	0.14	0.40	1.00			
Cortisol	0.08	0.16	0.61	1.00		
Lactate	0.47	0.13	0.33	0.24	1.00	
Mel Blood	-0.53	0.11	0.22	-0.03	-0.31	1.00

r-values from Pearson product-moment correlations
6 rows not used due to missing values

Table 3.6 Correlation Matrix Using Pre-Exposure Blood Samples Without Subject 7

Variable	Duration	NE	Epi	Cortisol	Lactate	Mel Blood
DUR	1.00					
NE	0.26	1.00				
Epi	0.16	0.43	1.00			
Cortisol	-0.01	0.21	0.61	1.00		
Lactate	0.54	0.17	0.37	0.24	1.00	
Mel Blood	-0.65	0.14	0.22	-0.02	-0.40	1.00

r-values from Pearson product-moment correlations
4 rows not used due to missing values

It was noted from Figure 3.7 that subject # 7 had an unusually high pre-exposure melatonin level when compared to the other subjects. Since this subject had very low G-tolerance duration and very high melatonin, it was believed that his data may have obscured the true relationship between duration and the pre-exposure level of melatonin. Therefore, an additional correlation matrix was computed excluding subject # 7, as shown in Table 3.6. The correlation between melatonin and duration improved from –0.53 to –0.65.

4. DISCUSSION

Circadian Effect

The hypothesis that there is a practical difference between day and night G tolerance was not statistically supported. If these results are substantiated, the Air Force should feel confident about sending pilots to fly and fight at night with minimum adverse effects on their G tolerance. However, one should be somewhat cautious in applying these findings for three reasons.

First, based on previous studies that also tested subjects' G-tolerance duration with the 4.5 to 7 G simulated air combat maneuvering (SACM) profile, we did not expect the variability of G-duration among subjects to be as large as we have found (105.2 seconds for the night run and 113.4 seconds for the day run). In particular, Epperson's study (1982) showed the variability of SACM tolerance time of three test groups, with 7 to 9 subjects in each group, to range from 65.6 to 109.5 seconds. Also, in Burton's study (1987), a group of 7 subjects had standard deviation of their SACM tolerance time to be 44.4 seconds. Furthermore, Besch et al. (1994) showed a group of 7 subjects to have standard deviation of their SACM tolerance time to be 41.5 seconds. It was thought that if the variability in our study was closer to the ones listed above, we would have detected a difference, if there were any, between daytime and nighttime G tolerance.

When we compared the coefficient of variation from each of those studies to our own, as shown in Table 4.1, we found that the three Epperson groups were not

significantly different from our study, but the Besch and Burton studies were significantly different from ours at the 0.05 level. Upon closer examination of Besch's experimental protocol, it was noted that the test subjects had additional G-exposures, 4 to 6 minutes prior to the SACM test, which may have fatigued the subjects, and may account for the lower subject duration and variability. The additional G-exposures consisted of a 30-second exposure at 3 G's, followed 2-minute rest and a gradual onset exposure, at 0.1G/second, to a G level where the subject experienced 100% peripheral light loss. The mean tolerance duration for the SACM exposure in the Burton study is less than what is usually found for exposures of this type. Burton reviewed six other research studies and found the range for SACM tolerance to be from 102 to 245 seconds. In effect Burton study was on the lower end of this range. Based on closer examination of studies by Epperson, Besch, and Burton, we conclude that the variability encountered in our study may be large, but is not excessive.

Table 4.1 Comparison of Variability

Researcher	**N**	**Mean**	**SD**	**CV**	**F***	**Crit. F****	**Significant?**
Epperson	9	225	109	.48	1.07	3.39	no
Epperson	7	180	96	.53	1.39	4.10	No
Epperson	8	191	66	.35	2.93	3.68	No
Besch	7	230	42	.18	7.24	4.10	.05
Burton	6	112	44	.39	6.60	4.78	.05
Wright (D)	10	320	113	.35	1.16	3.18	No
Wright (N)	10	319	105	.33			

* Ratio of Wright variance to other studies

** 5% critical value of F

CV = SD/mean

Second, we should be somewhat cautious about recommending that Air Force can feel confident about sending pilots to fly at night with minimum adverse effects on their G tolerance because two out of four subjects who performed better at night had unique circumstances that may have affected their performance. Subject #4 worked out at the gym prior to her night test and commented after her nighttime test that she still felt "pumped up" from that workout. This night performance was recorded as her personal best centrifuge duration test to date. Subject # 8 had a female friend present at the centrifuge area for his nighttime test. After the test, the subject admitted to the researchers that he probably "pushed a little harder" because she was present. This nighttime run was also his personal best centrifuge duration test to date. The question is whether these subjects were equally motivated for their daytime runs.

Two more questions should be considered for all four subjects who performed better at night: Did these people routinely stay up past 2300 hours? Were they being tested at their circadian trough in their personal performance, or did some of these subjects have their circadian cycles slightly shifted, and their nighttime testing occurred at a time when they would have been awake anyway? Because these subjects were military members and/or civilian contractors working on a military base, it was assumed that they would normally rise between 0500 and 0600 hours and go to bed about 2300 hours. Perhaps that assumption was not realistic for some of these subjects.

Third, an age bias may have existed: a significant portion of the fighter pilot population is in their 30's and even some in their 40's. The average age of the subjects in this study was 27.8 years, with the oldest being 36. While there are older individuals in

the School of Aerospace Medicine Centrifuge subject pool, none of them were available or willing to participate in this test.

Sequence Effect

Even though no significant treatment effect was found between G tolerance (duration) and time of day, there was a significant sequence effect from the first run to the second run regardless of the time of day for the first run. Would subjects improve even more if required to have third or fourth run, or would the sequence effect diminish?

Inadvertently, this question may have been partially answered with subject #4. This 29 year old female terminated her first nighttime session at 72 seconds because she thought that the "tingling in one of her feet" and "feeling somewhat fatigued" was an adequate reason to stop. After the medical observer and the investigators discussed the circumstances, they decided that these symptoms did not meet the normal termination requirements of the protocol and that the subject should be allowed to start anew and the aborted session should be considered as additional practice time. The subject was restarted with another group and only her last two sessions were included in the data. When her data collection sessions began a couple of weeks later, her daytime session was a good performance (218 seconds), then she recorded a "personal best" for duration (375 seconds) during the nighttime session. It is possible that this additional practice time allowed her to improve her G tolerance in subsequent runs, and that the other subjects would have shown similar improvements if they were allowed additional practice sessions.

Melatonin

In our study nighttime melatonin levels were generally lower than expected (see Figure 3.7 and Table 3.1). This may be due to subjects being exposed to normal ambient lighting (180 lux) in the laboratory during their nighttime sessions. Researchers such as Wever (1989), Dawson et al. (1992), Van Cauter et al. (1994), and Duffy et al. (1996) have demonstrated that bright light (1000-1200 lux) suppressed melatonin production, but dim light (<100 lux) did not. However, there may be evidence that lower light intensity could also suppress melatonin production. Reiter and Richardson (1992) claimed that there was a dose response relationship between light exposure and melatonin suppression. Also, Boivin et al. (1996) reported that relatively low intensity indoor room light (180 lux) significantly phase shifted the human temperature rhythm. It is possible that if our subjects stayed in dim light (<100 lux) prior to and during their nightime G-sessions, their melatonin levels may have been higher, their nighttime G-tolerance duration could have been shorter, and a stronger negative correlation might have been seen between melatonin and G-tolerance duration.

Athletic Performance

The test subjects' level of physical conditioning does not appear to be a good determining factor in predicting circadian differences in G tolerance. The subjects that participated in this study were a good cross section of athletic ability and centrifuge experience: between 22 to 1500 runs. In addition to being regular participants as test subjects in several different centrifuge experiments, each subject was in good enough

physical condition to pass a rigorous Air Force Flying Class III Physical. When subjects were divided into two groups, those who performed better during the day, and those who performed better at night, there was no recognizable trend for the level of physical conditioning to dominate either group. While performance differences of 10% or greater were found between day and night, the direction of that change was not consistent. This contradicts studies by Hill (1992), Hill and Smith (1991), and Reinberg (1988), who found that afternoon performance was better than late night/early morning performance. Perhaps, as Atkinson and Reilly (1996) suggested, inadequate test/retest reliability explains the apparent differences in circadian performance rhythms.

Additional analyses of the data (see Table 3.3) have shown that subjects exerted a considerable amount of effort during their test runs, as evidenced by post test elevation in blood concentrations of NE, cortisol, and lactate. The elevations of cortisol and lactate in response to exercise are well documented and were not unexpected. In particular, highly significant elevations in blood lactate levels confirmed findings from Burton (1987) that subjects were highly anaerobically stressed while performing the anti-G straining maneuver (AGSM). The elevation seen in NE confirms the findings of previous studies by Lehmann (1982), Mills (1985), and Tauri (1991), who found that higher physical workloads elevated NE preferentially. However, the elevations in these stress hormones and in lactate (in response to the physical demands of withstanding the G forces) are of limited value in terms of developing a test we can give to the pilots before they fly, as shown by relatively low correlations in Table 3.4. In summary, we can tell if

a pilot has endured high levels of physical stress after he/she has experienced it, but we still do not have a simple procedure to predict their ability to withstand G stress.

Sleep Loss and Fatigue

In order to control for the interference of sleep and to equate the nighttime and daytime test G sessions in terms of total sleep time, subjects were given specific criteria for sleep times. However, as reported in the Results section, subject # 9 did not adhere to the requirements of this test protocol and his data was eliminated from the analyses. He was nonetheless a very instructive case study in terms of factors that effect G tolerance. This subject got very little sleep and was in an extremely high stress situation, due to college final exams, for the 3 days prior to his daytime test session, during which he lasted only 199 seconds. However, the following week, the subject was no longer under excessive stress and was getting at least 8-10 hours of sleep at night for the previous 3 nights prior to his nighttime test session. This time he was able to last 590 seconds. Based on this subject, it appears that physical stressors such as lack of sleep and/or extreme levels of stress may have a larger impact on G tolerance than does the proposed circadian effect. A more in depth look into the sleep loss and fatigue factors will be presented in the section to follow.

5. CONCLUSIONS AND RECOMMENDATIONS

Circadian Effect

This study has attempted to determine whether there is a practical difference between day and night G-tolerance (hypothesis 1) in order to warn pilots of possible adverse consequences due to circadian effects. Even though circadian variation in athletic performance has been shown to have potentially significant performance consequences for the athlete, we did not find evidence from the centrifuge study to support the above hypothesis.

This study leads one to conclude that if there is a circadian effect on a pilot's G-tolerance, it is a small one, or this study would have shown it. The subjects' G-tolerance testing times were selected in order to highlight the potential maximum circadian differences. Since no such difference was seen, it may be safe to conclude that this effect is indeed very small and the Air Force should feel more confident to send pilots to fly and fight at night. However, other influences did seem to have larger effects on pilots' G-tolerance. Unique circumstances encountered by three subjects during this study (the residual effect from a work out, possible psychological impact from the presence of a significant companion, and the effects of sleep loss and fatigue) may have effected their G-tolerance. In the future studies, subjects' motivation for centrifuge runs should be even more closely monitored and external influences should be even more strictly controlled.

Future studies should also continue the pursuit of subjects with a wide range of ages in order to apply the results to the active flying population as a whole. In particular, they need to include older fliers, 30 years old and up, in order to determine if they are more or less influenced by circadian or other factors. These pilots would generally be more senior in rank and therefore would probably not fly as often as their junior counterparts. However, when they fly, their susceptibility to circadian factors should be understood.

To compensate for the large variability in G tolerance duration among subjects we have encountered in this study, it appears that more subjects are needed for future studies. A post-hoc power analysis on the data, using an alpha level of 0.05, shows that in order to detect a 30-second difference in duration between day and night tests (delta level), 46 to 64 subjects are needed, assuming that the standard deviation is between 100 to 120 seconds (sigma level). The limits for the sigma level were selected to include the standard deviations seen in this study (105.2 to 114.2). The 30-second difference in duration was chosen because it represents one complete cycle of the simulated air combat maneuvering profile (SACM: 15 seconds at 4.5 G's, 15 seconds at 7 G's) used in the centrifuge tests, and because it would be an easy difference to see. Additionally, air combat experience since WWII has shown that "dogfights" usually last no more than a few minutes. Practically speaking, the last 30 seconds in a "dogfight" could include the last couple of high G turns a pilot must perform in order to make the "kill." Table 5.1 shows the range of the least significant number of subjects (LSN) needed at various levels of sigma and delta.

Table 5.1 Subjects Needed for a Given Level of Sigma and Delta

Alpha significance level	Sigma sd of the error	Delta effect size	LSN: Least significant number
0.05	100	10	386.6
		20	98.5
		30	45.2
		40	26.6
		50	18.0
		60	13.4
	110	10	467.2
		20	118.7
		30	54.1
		40	31.6
		50	21.2
		60	15.6
	120	10	555.6
		20	140.7
		30	63.9
		40	37.1
		50	24.7
		60	18.0

Obviously, looking for a 10 second difference between day and nigh G tolerance, at the standard deviations observed in this study, would require unacceptably large sample sizes (n=387 to 556) and should not be considered. However, differences of 30 seconds or greater are more reasonable to pursue from a practical and financial standpoint.

Sequence Effect

To control for the sequence effect found in this study, perhaps a more effective design would have been to include 4 trials per subjects in random order: two trials during day and two during night. Also, since most subjects for centrifuge studies participate in

more peak-G experiments as opposed to maximum duration experiments, perhaps having more practice sessions doing the simulated air combat maneuvering (SACM) profile until exhaustion, before testing, would be helpful in eliminating the sequence effect. Indeed, when Epperson (1982) examined the influence of different methods of physical conditioning on subjects' SACM duration, he devoted five weeks to training them. The real issue may not be so much a sequence effect, as it is making sure subjects are adequately familiarized with the demands of the SACM profile.

Athletic Performance and Blood Components

Because there were no statistically reliable correlations between pilots' G-tolerance and their pre-test concentrations of selected hormones in the blood samples analyzed in this study (hypothesis 2), no valid regression equations were formulated to predict pilots' G-tolerance. Analyses of blood components in future studies should continue to look at norepinephrine, epinephrine, cortisol, and melatonin; however, the cost of these tests should be carefully considered. At this time, the melatonin assay is more expensive than norepinephrine, epinephrine, or cortisol combined. Additionally, research on the effect of lighting on supression of melatonin prior to a nightime mission should be further investigated. Moreover, since aircraft technology continues to advance, and pilots are forced to operate closer to their limits than ever before, we must continue looking for a simple procedure to predict their ability to withstand G stress.

Sleep Loss and Fatigue

As discussed previously, it appears that other physical stressors such as lack of sleep and/or extreme levels of stress may have a larger impact on G-tolerance than does the proposed circadian effect.

A large body of research information focusing on sleep and performance already exits and can be applied to the flying population. In the textbook *Biopsychology* by Pinel (1993), the author explains that there are at least three credible theories regarding the purpose and mechanisms for sleep and fatigue: the recuperative theory, the circadian theory, and the combination recuperative/circadian theory. The recuperative theory asserts that being awake disrupts the homeostasis of the body and sleep is required to restore it. The longer a person is awake, the larger the disruption and the greater the desire is to go to sleep. The circadian theory asserts that a neural mechanism encourages an animal to sleep during the time of day when they aren't engaged in activities necessary for survival. Sleepiness will grow or diminish in a sine wave fashion according to a circadian factor (time of day), with sleepiness being greatest at times when we normally sleep. A night of sleep loss would simply be ignored once the sun is up and we begin the normal daily routine. The recuperative/circadian theory was proposed by Borbély (1984). It combines effects of both the recuperative and circadian models.

One's own experience and fatigue research confirm that sleep does have components of both the recuperative and circadian theories. If you have ever stayed up all night working or studying, you know that the hardest time to stay awake is between

0200 and 0500 hours. However, after the sun comes up, the desire to sleep diminishes. The desire to sleep doesn't diminish to the point where one feels as though they had a full night's sleep, but it doesn't feel as bad as the middle of the night, either. These changes in subjective fatigue were demonstrated by French et al. (1994) in a study of a 36-hour mission in a B-1B simulator. The mission began about 2200 hours local time and subjective fatigue ratings increased during the night but markedly diminished in the morning and rose again the next night.

A more recent study by Chelette et al. (1998) saw a lack of effect on overall performance of 24 hours of sleep deprivation. However, in this study subjects who had been sleep-deprived for 24 hours were tested in the centrifuge at about 8 or 9 in the morning, at a point when the circadian theory would predict that their sleepiness would be diminishing. Perhaps there would have been a greater effect if the subjects were tested closer to the point in their circadian cycle when they would have normally been sleeping and their performance might have been worse. Nonetheless, a complex flying task in the centrifuge was only half as likely to be successfully completed in a sleep deprived condition suggesting that sleep loss and circadian effects combined have larger effect than any one individually.

The theories of sleep combined with the findings of French (1994) and Chelette (1998) bring to mind this question: Can the performance deficits from sleep loss and fatigue be offset with pharmacological interventions?

Pharmacological methods have been used both to combat fatigue and to promote sleep in various arenas including military aviation. Stimulants such as caffeine,

dextroamphetamine, and modafinil have been used to promote vigilance. Conversely, sedatives such as alcohol, benzodiazapine, and melatonin have been used to promote sleep when desired. Until larger definitive studies fully describing the circadian impact on pilot G tolerance have been accomplished, several pharmacological interventions may be considered for use in the flying arena to further minimize the impact of circadian effects on pilot G tolerance.

Caffeine is a compound found in coffee, tea, and many soft drinks. Lieberman (1992) found that caffeine had a positive effect on vigilance, and simple and complex reaction times. However, it is a diuretic that may increase dehydration for flyers on long trips. Moreover, too much caffeine can produce anxiety, disturbed sleep, and psychophysiological complaints.

Dextroamphetamine first saw operational use by both British and Axis powers in the Second World War. Low doses of 5 mg every 4 hours maintained pilot alertness and performance without significant side effects. Emonson and Vanderbeek (1995) reported that dextroamphetamine was used by tactical flyers as recently as the Desert Shield and Desert Storm operations during the Gulf War without major side effects. Their conclusion was that "amphetamine use enhanced cockpit performance and flight safety by reducing the effect of fatigue during critical stages of flight." However, as of this writing, the military seems to be undecided on the issue of using drugs to augment crew performance.

Modafinil is a relatively new stimulant produced by Lafon Labs of Maisons-Alfort, France. It is used to treat narcolepsy, sleep attacks, and hypersomnia, but there is

considerable potential for use of this compound in a military setting. Lyons and French (1991) reported claims by noted sleep researcher Michel Jouvet that modafinil "could keep an army on its feet and fighting for three days and nights with no major side effects." It has few side effects, doesn't appear to produce tolerance, and has been used for up to 3 years in clinical treatments for narcolepsy and hypersomnia. Furthermore, they recommended that military labs include modafinil when studying sustained performance in the future. Lagarde et al. (1995) evaluated eight individuals taking 200 mg of modafinil every 8 hours for 60 hours of total sleep deprivation. They report a satisfactory level of subjective and objective vigilance, and a total absence of microsleep. Finally, Buguet et al. (1995) studied the effect on sleep after 64 hours of sleep deprivation. They found that the group that had used modafinil during the deprivation phase had sleep patterns close to that of the placebo group. Additionally, there was a decreased need for a long recovery sleep usually needed to compensate for the lost sleep due to total sleep deprivation

Alcohol is used as a sedative to initiate sleep but its use is not advisable. Sleep quality is poor and performance deficits are noted during the subsequent wake state (Zarcone, 1994).

Benzodiazapines have been used to treat sleep disorders and insomnia. Short acting benzodiazapines, such as temazepam and triazolam, were shown by Nicholson et al. (1985) to be more applicable to military operations that require a short-acting hypnotic. French et al. (1990) demonstrated that transient insomnia during military surge operations could be minimized using temazepam without adversely effecting operational

effectiveness. Currently, temazepam is the only medication the U.S. Air Force allows to be prescribed for treatment of transient insomnia in operational aircrew.

Melatonin normally has its highest concentration in the blood (its acrophase) at night. Taking an additional amount prior to bed may help promote sleep. Dollins et al. (1994) found that melatonin administered in 1-10 mg doses decreased the amount of time subjects took to fall asleep, and it increased sleep duration. They concluded that melatonin might be as effective a hypnotic as the benzodiazapines. Additionally, melatonin may be helpful in treating jet-lag symptoms. Claustrat et al. (1992) found that it did alleviate the jet-lag symptoms of morning fatigue and evening sleepiness. Melatonin is available commercially as an over-the-counter drug, but because there are no military performance studies yet published, it cannot be used by operational aircrew.

Pharmacological interventions have been used in laboratories to promote or inhibit sleep as desired. However, their use in military flying operations must be approached with caution. We must carefully evaluate both the short term and long term benefits against the potential deleterious consequences. At the very least, we need to guard against over reliance on drugs and prevent the aviation community's motto from becoming "better flying through chemistry."

Summary of Recommendations

Based on the information presented in this paper, the reader should consider the following recommendations:

- The Air Force should be more confident about sending pilots to fly and fight at night knowing that there is not a major circadian effect on their performance.
- In future studies the researchers should:
  - -- enforce a strict sleep/activity cycle for test subjects to follow during testing and closely monitor external influences on subjects' motivation.
  - -- include older subjects (30 years old and up).
  - -- include more subjects to compensate for large variability seen in longer G-tolerance duration.
  - -- include 4 trials per subjects and/or more practice sessions during the simulated air combat maneuvering (SACM) profile until exhaustion.
  - -- include norepinephrine, epinephrine, cortisol, and melatonin with careful consideration for cost versus benefit.
  - -- investigate the effect of lighting on nighttime G-tolerance duration
- We should consider pharmacological interventions in the flying community to promote sleep or alertness, but with extreme caution.

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VITA

Bruce Alan Wright, Major, USAF, BSC
Department of Aerospace Physiology and Human Performance
USAF School of Aerospace Medicine
2602 West Gate Road, Brooks AFB TX 78235-5252
bwright@samafc.brooks.af.mil

Education

Ph.D. in Interdisciplinary Engineering, December 1998, Texas A&M University
M.S. in Industrial Engineering, May 1990, Texas A&M University
B.S. in Physiology, May 1983, University of Illinois

Experience

Human Factors Engineer, Research Physiologist Brooks AFB, USAF School of Aerospace Medicine	8/98
Ph.D. Candidate Texas A&M University, College of Engineering	7/95 to 8/98
Assistant Professor, Laboratory Director US Air Force Academy, Department of Psychology	9/92 to 7/95
Special Projects Physiologist/Human Factors Engineer Edwards AFB, Flight Test Engineering	8/90 to 9/92
Graduate Student Texas A&M University, Department of Industrial Engineering	7/88 to 8/90
Chief of Operations, Human Centrifuge and Altitude Chamber Brooks AFB, Armstrong Aeromedical Research Laboratory	7/86 to 7/88
Aerospace Physiology Instructor Mather AFB, Undergraduate Flying Training Unit	5/83 to 7/86